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A phase I study of obatoclax mesylate, a Bcl-2 antagonist, plus topotecan in solid tumor malignancies

Paul K. Paik,
Thoracic Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA

Charles M. Rudin,
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

Andrew Brown,
Thoracic Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA

Naiyer A. Rizvi,
Thoracic Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA

Naoko Takebe,
Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Rockville, MD, USA

William Travis,
Thoracic Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA

Leonard James,
Thoracic Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA

Michelle S. Ginsberg,
Thoracic Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA

Rosalyn Juergens,
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

Susan Markus,
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

Leslie Tyson,
Thoracic Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA

Sara Subzwari,
Thoracic Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA

Mark G. Kris, and

Correspondence to: Lee M. Krug.

Thoracic Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA

Lee M. Krug
Thoracic Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA, krugl@mskcc.org

Abstract

Purpose—To establish the safety, maximum tolerated dose (MTD), recommended phase II dose, and preliminary anti-tumor activity of obatoclax mesylate (GX15-070MS), a Bcl-2 antagonist, in combination with topotecan in patients with solid tumor malignancies.

Patients and methods—Patients with solid tumor malignancies for whom topotecan was an appropriate treatment were administered obatoclax mesylate and topotecan on a 3-week cycle in a pre-defined, standard 3 + 3 dose escalation scheme. The starting dose for obatoclax mesylate was 14 mg/m^2 by 3-h intravenous (IV) infusion. Topotecan 1.25 mg/m^2 was given concurrently as an IV infusion on days 1–5 of each cycle.

Results—Fourteen patients received 40 cycles of obatoclax mesylate at the following doses: 14 mg/m^2 on day 1, 14 mg/m^2 on days 1 and 3, and 20 mg/m^2 on day 1. The most common toxicities related to obatoclax were neurologic, including ataxia, mood alterations, somnolence, and cognitive dysfunction. The majority of these were grades 1 and 2 (88%). Two of five patients experienced dose-limiting grade 3 neurologic toxicity at a dose of 20 mg/m^2; no patients experienced grade 4 neurologic toxicities, and no other patients experienced grade 3 neurologic toxicity. Of the patients who experienced grade 3 neurologic events, one later developed febrile neutropenia, which was also a dose-limiting toxicity (DLT). After an additional three patients were treated without DLT at the previously tolerated dose of 14 mg/m^2 on day 1, the level was escalated to 14 mg/m^2 on days 1 and 3. Three patients were treated at this dose and, with none experiencing a DLT, 14 mg/m^2 on days 1 and 3 was defined as the recommended phase II dose. Two patients with small-cell lung cancer (SCLC) achieved partial responses and four patients had stable disease. Median time to progression (TTP) was 12 weeks.

Conclusion—Obatoclax mesylate administered at 14 mg/m^2 IV on days 1 and 3 is safe and well tolerated when given in combination with topotecan 1.25 mg/m^2 IV on days 1–5 of an every 3-week cycle. A phase II trial to assess the efficacy of this combination for patients with relapsed SCLC is currently accruing patients.

Keywords

Small-cell lung cancer; Obatoclax mesylate; Topotecan; Apoptosis

Introduction

Though malignant transformation of the normal cell can occur through a wide range of biologic mechanisms, evasion of programmed cell death is a common, obligate denominator in each. Apoptosis can be triggered both by extrinsic death-receptor signaling and by intrinsic pathways, such as those elicited by genomic damage [1]. Many cancer types have been found to upregulate factors inhibiting apoptosis, most notably anti-apoptotic members of the Bcl-2 family, such as Bcl-2, Bcl-XL, and Mcl-1. These anti-apoptotic factors bind and inhibit the key pro-apoptotic Bcl-2 family members Bax and Bak, which if released, initiate an irreversible cascade of programmed cell death signaling through mitochondrial membrane disruption and cytoplasmic release of factors including cytochrome c. The anti-apoptotic Bcl-2 family members also interact with a third class of Bcl-2 family members, the BH3-only proteins such as Bad, Bim, and Bid [2]. BH3-only proteins are activated by both extrinsic and intrinsic

apoptotic triggers and bind to the anti-apoptotic Bcl-2 family members, releasing Bax and Bak and thereby promoting apoptosis [2]. Structurally, Bcl-2 contains three distinct Bcl-2 homology (BH) regions: BH1, BH2, and BH3. These regions fold to form a globular domain that contains a hydrophobic groove into which the BH3 domain of the pro-apoptotic family members can bind [3].

The convergence of many different cytotoxic stimuli onto Bcl-2 and the specific upregulation of Bcl-2 in a variety of cancers have made inhibiting its function an attractive therapeutic target. Both peptide and non-peptide BH3 mimetics have been shown to be effective in vitro in inhibiting dimerization of Bcl-2 and Bcl-XL with their pro-apoptotic counterparts, shifting the balance toward apoptosis [3]. Obatoclax mesylate (GX15-070MS) is a small molecule, which may function in part as a BH3-mimetic to promote apoptosis by inhibiting this interaction. Obatoclax mesylate induces cell death in nanomolar concentrations in a wide range of cancer cell types in vitro, including non-small-cell lung, prostate, colon, cervical, breast, and ovarian [4]. Additive cytotoxicity when combining obatoclax mesylate with standard chemotherapy was demonstrated in in vitro studies of mantle cell lymphoma [5]. Synergy between obatoclax mesylate and cisplatin was also reported in non-small-cell cancer cell lines, associated with an inhibition of Mcl-1: Bak interaction [6]. Single-agent anti-tumor activity has also been seen in mouse xenograft models of cervical, prostate, breast, and colon cancer [4].

Small-cell lung cancer (SCLC) is an aggressive subtype of lung cancer, which, relative to non-small-cell lung cancer, has a shorter doubling time, higher growth fraction, and tendency for the earlier development of widespread metastases. A major clinical challenge in SCLC is the short time to relapse following initial chemotherapy. While first-line treatment with cisplatin and etoposide has an overall response rate of 60–80%, fully half of these patients relapse by 24 weeks [7]. Existing second-line treatments are considerably less effective, with a median survival of 4–6 months following recurrence.

Pre-clinical data suggest that a primary mechanism of chemotherapeutic resistance may be driven by Bcl-2 expression; indeed, 69–90% of all SCLC tumors are found to over-express Bcl-2 [8–11]. In SCLC cell lines, Bcl-2 antisense oligodeoxynucleotides decreased Bcl-2 levels and promoted apoptosis, both alone and synergistically in combination with chemotherapy [12,13]. Bcl-2 may also rescue SCLC cells driven by other oncogenes, such as c-myc, from the cell death that would otherwise ensue [14].

Topotecan is the only drug currently approved by the United States Food and Drug Administration for treatment of recurrent SCLC after first-line platinum-based therapy. Topotecan is a semi-synthetic derivative of camptothecin, possessing topoisomerase I inhibitory activity. Like other DNA-damaging agents, topoisomerase inhibitors trigger a DNA damage-mediated apoptotic signaling pathway that can be inhibited by Bcl-2. In light of data supporting the added benefit of Bcl-2-targeted therapy to standard chemotherapy, and given their non-overlapping toxicities and potentially synergistic mechanisms of action, we combined obatoclax mesylate with topotecan in a phase I study of patients with relapsed SCLC and other solid tumor malignancies for which topotecan was an appropriate treatment.

Patients and methods

Patient selection

Men and women ≥18 years of age with a Karnofsky performance status of ≥70% and with histologically or cytologically confirmed solid tumors for which topotecan was an appropriate treatment were eligible. Patients with progressive brain metastases, leptomeningeal involvement, and neurologic dysfunction other than peripheral neuropathy were excluded given the need to accurately assess neurologic adverse events associated with obatoclax

mesylate. Any number of prior chemotherapy or radiation treatments was allowed, with the last treatment given ≥4 weeks prior. Normal organ and bone marrow function was required, defined as a leukocyte count ≥3,000/μL, absolute neutrophil count ≥1,500/μL, platelets ≥100,000/μL, total bilirubin within institutional normal limits, AST and ALT ≤2.5 times institutional upper limit of normal, and a creatinine clearance ≥60 mL/min/1.73 m^2. While obatoclax mesylate has a low potential to inhibit drugs metabolized by CYP1A2, CYP2C19, and CYP3A4/5, efforts were made to change enzyme-inducing medications to non-inducing drugs. A list of commonly prescribed CYP1A2, CYP2C19, and CYP3A4/5 substrates, inhibitors, and inducers was provided as an appendix to the study protocol for cross-referencing patient medication lists during the eligibility review process. A suitable non-interacting replacement drug was substituted when available. Pregnant patients were excluded, as were patients with uncontrolled comorbid conditions. All patients signed an informed consent document prior to participation in the study.

Study design and treatment

Participating centers included Memorial Sloan-Kettering Cancer Center and the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. This was a phase I, open-label, dose escalation study. A standard 3 + 3 dose escalation design was used. Four cycles of therapy were planned, though patients could continue on treatment if deemed appropriate by the treating physician. Patients were treated until time of disease progression, limitation from an inter-current illness, unacceptable adverse event, consent withdrawal, or treatment delay of ≥22 days due to toxicity. Obatoclax mesylate was generously provided by GeminX, Biotechnologies, Inc. and the National Cancer Institute.

Based on prior phase I dose escalation studies of obatoclax mesylate, four dose levels were initially planned, including 14 mg/m^2 on day 1, 20 mg/m^2 on day 1, 14 mg/m^2 on days 1 and 3, and 20 mg/m^2 on days 1 and 3 of an every 3-week cycle [4]. Following the start of the study, interim data were released from a phase I study of obatoclax in patients with advanced hematologic malignancies in which no formal MTD was reached despite escalation to 28 mg/m^2 on days 1–4 of an every 2-week cycle [15]. In addition, multi-day dosing appeared to have no greater grade 3/4 toxicity than single-day dosing. In light of this information, an amendment to the protocol by the NCI allowed for a reclassification of the 14 mg/m^2 days 1 and 3 dose level as interim to the 14 and 20 mg/m^2 single-day doses (Table 1).

Obatoclax mesylate was given as a 3-h infusion based on data suggesting a reduced frequency of dose-limiting toxicities (DLT) compared to a 1-h infusion. The clinical pharmacokinetics at these doses correlate with AUC values that produced antitumor activity in pre-clinical mouse models. Topotecan was given at a dose of 1.25 mg/m^2 on days 1–5 of each 3-week cycle. This dose was selected to mitigate the hematologic toxicities associated with topotecan at the initially studied dose of 1.5 mg/m^2 while preserving its efficacy, as reported elsewhere [16, 17]. Growth factor support (pegfilgrastim, Neulasta) was additionally provided on day 6, 7, or 8 to offset neutropenia.

Patients were pre-medicated with dexamethasone 10 mg IV, diphenydramine 50 mg IV, and ranitidine 50 mg IV before each dose of obatoclax mesylate to prevent a hypersensitivity reaction characterized by the rapid onset of severe pain that has been previously described. Standard anti-emetics (palonosetron or dolasetron) were provided before each dose of topotecan. Patients were monitored with serial neurologic examinations during the obatoclax infusion and for at least 1 h after the end of infusion.

Assessments

Pretrial screening was performed within 7 days of initial treatment. During treatment, patients were evaluated on days 1, 8, and 15 of each 3-week cycle with physical examination (including vital signs and neurologic evaluation) and blood work (complete blood count, metabolic panel, and liver function tests). Adverse events (AE) were graded utilizing the NIH CTCAE scale, version 3.0. Hematologic DLTs were defined as ≥grade 3 treatment-related thrombocytopenia for ≥14 days, neutropenia for ≥7 days despite treatment with pegfilgrastim, and ≥grade 3 neutropenia with fever (≥38.5°C) or clinically documented infection. Non-hematologic DLTs were defined as ≥grade 3 neurotoxicity, persistent grade 2 neurotoxicity not resolving to grade 1 by the next cycle, and any ≥grade 3 treatment-related non-hematologic toxicity considered by the investigator to be related or possibly related to the study drug. The maximum tolerated dose (MTD) was defined as the dose at which ≥2 of six patients experienced a DLT. The recommended phase II dose was defined as the highest dose level below the MTD.

Radiographic assessment for tumor response was performed every 6 weeks with CT imaging using RECIST v1.0. Patients with stable disease or response were allowed to continue. Confirmation of stable disease or response was required with a repeat CT scan performed ≥4 weeks from the preceding scan. Best overall response was defined as the best response from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since treatment initiation). Best response assignment required achievement of both measurement and confirmation criteria.

Results

Patient characteristics

A total of 14 patients were enrolled between October 2007 and October 2008. Patient characteristics are shown in Table 2. The most common tumor type was SCLC ($n = 8$), followed by extrapulmonary small cell ($n = 3$), pulmonary carcinoid ($n = 1$), Merkel cell ($n = 1$), and melanoma ($n = 1$). Patients were divided equally between men and women. The median number of prior chemotherapy regimens was two. Patients were enrolled at three dose levels, with 40 cycles of therapy completed in total. Seven of 14 patients completed all four planned cycles of treatment. Seven patients eventually withdrew from the study, six because of progression of disease, and one because of dose-limiting toxicity.

Dose-limiting toxicities and MTD

Dose escalation of obatoclax mesylate proceeded through a standard 3 + 3 dose escalation scheme. The dose of topotecan remained constant at 1.25 mg/m^2 on days 1–5. Three patients were accrued to the initial dose of 14 mg/m^2 day 1, none of whom experienced a DLT. The dose was then escalated to 20 mg/m^2. Of the initial cohort of three patients, one experienced a DLT in the form of grade 3 somnolence and speech impairment (Table 3). As per protocol, the cohort was expanded to up to six patients. After two additional patients were enrolled, one experienced grade 3 mood alteration, ataxia, and febrile neutropenia (Table 3). With 2 out of 5 patients experiencing a DLT, the dose of 20 mg/m^2 was declared the MTD. The dose was subsequently reduced to the previously tolerated level of 14 mg/m^2 day 1 and an additional three patients accrued, none of whom experienced a DLT.

Three patients were then recruited to a final dose level of 14 mg/m^2 on days 1 and 3. Again, none experienced a DLT. One patient required a dose-reduction to 10 mg/m^2 during cycles 2–4 due to creatinine clearance changes unrelated to either obatoclax mesylate or topotecan. The recommended phase II dose for obatoclax mesylate in combination with topotecan 1.25 mg/m^2 days 1–5 was thus determined to be 14 mg/m^2 on days 1 and 3 of an every 3-week cycle.

Adverse events

Neurologic toxicities were the most common category of adverse event (AE) seen in this study, comprising 50% of all AEs recorded. Most patients experienced some form of transient neurologic AE that began 15–30 min after the start of obatoclax mesylate infusion and resolved within 1–2 h after treatment end. Toxicities included ataxia, mood alterations (depression, euphoria), somnolence, speech impairment, and cognitive disturbances. The majority of these adverse events were grades 1 or 2 (88%). Two patients at the 20 mg/m^2 dose level experienced grade 3 neurologic toxicities, one with somnolence and speech impairment, and the other with ataxia and mood disturbance. There were no grade 3/4 neurologic toxicities at either the 14 mg/m^2 day 1 or 14 mg/m^2 days 1 and 3 dose levels.

Hematologic toxicity was seen at each dose level as expected with topotecan (Table 4). Four grade 3/4 hematologic AEs were seen at the 14 mg/m^2 day 1 dose, 3 at the 14 mg/m^2 days 1 and 3 dose, and 7 at the 20 mg/m^2 dose. Of the 7 grade 3/4 hematologic AEs at the 20 mg/m^2 dose, three were grade 3 anemia (60%), two were grade 3/4 thrombocytopenia (40%), and one was febrile neutropenia, which was a DLT. No other hematologic DLTs in any cohort were documented. Grade 4 thrombocytopenia was seen in one patient at each of the other dose levels.

The most frequent non-hematologic toxicities were fatigue and nausea, though almost all of these were grade 1/2 (95%). A single episode of grade 3 nausea occurred in one patient at the 14 mg/m^2 day 1 dose level. No other grade 3/4 non-hematologic AEs were reported at any dose level.

A hypersensitivity reaction responsive to steroid and H2-blocker administration was seen in one patient treated at 20 mg/m^2.

Antitumor activity

Of the 14 patients enrolled, 13 were evaluable for response. One patient withdrew from the study prior to the first response assessment due to febrile neutropenia. Of these 13 patients, 2 developed a partial response (PR) and 4 developed stable disease (SD). Both partial responders and 3 of the 4 patients with stable disease had diagnoses of SCLC. One patient with pulmonary carcinoid maintained stable disease for all four cycles of treatment. No complete responses were observed. The median time to progression (TTP) was 12 weeks.

Discussion

Because over-expression of Bcl-2 is known to interfere with the cytotoxic effects of chemotherapy, it has been of great interest to assess the potential therapeutic synergy between Bcl-2 antagonists and standard chemotherapies. To that end, we demonstrated that obatoclax mesylate given at a dose of 14 mg/m^2 on days 1 and 3 of an every 3-weeks cycle together with topotecan 1.25 mg/m^2 on days 1–5 is a safe and well-tolerated treatment in patients with relapsed SCLC and advanced solid tumor malignancies.

In particular, while obatoclax mesylate has not been known to have significant bone marrow toxicity, it was important to demonstrate that the combination of obatoclax and topotecan was not prohibitively myelosuppressive. Historically, rates of grade 3/4 hematologic toxicity with topotecan 1.25 mg/m^2 in previously treated patients range from 10 to 70% for neutropenia, 5–37% for thrombocytopenia, and 1–18% for anemia [16–18], with the higher rates of neutropenia and thrombocytopenia seen in patients previously treated with cisplatin. At the recommended phase II dose, only 1 of 3 patients (33%) experienced grade 3/4 hematologic toxicity, developing grade 3 neutropenia, grade 3 anemia, and grade 4 thrombocytopenia. None of these were dose-limiting, and, in the context of prior treatment with cisplatin-based therapy,

these toxicities did not exceed what would be expected with single-agent topotecan at 1.25 mg/m^2.

Neurologic toxicity is a known side effect of treatment with obatoclax mesylate, and indeed was the most common AE seen. Ataxia, mood alteration, and somnolence were the most frequent of the neurologic AEs experienced (33, 18, and 19%, respectively). Grade 3/4 toxicities were, however, uncommon, and seen exclusively in 2 patients treated at 20 mg/m^2. All neurologic AEs were transient as well, ceasing 1–2 h after the end of the infusion. In comparison with other phase I trials of obatoclax mesylate, the addition of topotecan did not appear to increase the prevalence of neurologic AEs [15,19]. The absence of similar neurologic toxicities in clinical evaluation of other Bcl-2 inhibitors studied to date suggests that this is an off-target effect.

Two of five patients experienced a DLT at a dose of 20 mg/m^2, meeting criteria for the definition of this dose as the MTD and requiring accrual of an additional three patients to the previously tolerated dose of 14 mg/m^2. Interim data from a phase I trial of obatoclax mesylate in patients with advanced hematologic malignancies similarly led to an amendment in the dose escalation design, allowing a final dose escalation to 14 mg/m^2 on days 1 and 3. With no DLTs experienced at this level, a dose of 14 mg/m^2 on days 1 and 3 was declared as the recommended phase II dose.

While the study was not powered to assess for efficacy, response assessment demonstrated partial responses in two patients and stable disease in four, with a median TTP of 12 weeks. Of these six patients, five were diagnosed with SCLC, including both partial responders. This rate compares favorably to historical overall response rates of between 9.2 and 21.7% seen with second-line topotecan in patients with SCLC [17].

In light of the recent phase I results of the more potent Bcl-2 inhibitor ABT-263, the modest hematologic toxicity of obatoclax mesylate in this study was notable. ABT-263 is a second-generation analog of the BH3-mimetic ABT-737, designed to overcome the poor oral bioavailability and solubility of the latter [20]. It retains a similar specificity profile to that of ABT-737, binding with low nanomolar affinity to Bcl-2, Bcl-XL, and Bcl-w, but less well to Mcl-1. Recent studies have highlighted Bcl-XL's role in protecting platelets from apoptosis, which is underscored by the rapid though reversible induction of thrombocytopenia in mice and dogs treated with ABT-737 [21,22]. Similarly, dose-limiting thrombocytopenia in 3/15 patients with CLL and dose-dependent reversible thrombocytopenia in all patients treated with ABT-263 were characteristic toxicities that emerged from the two phase I clinical trials of ABT-263 [23,24].

This toxicity stands in contrast to that seen in our study of combined therapy with topotecan, where 36% (5/14) of patients developed thrombocytopenia, a rate comparable to that of topotecan alone. This divergence is likely related to the disparate binding affinities of ABT-263 and obatoclax mesylate to the Bcl-2 family members [25]. While ABT-263 has strong preferential binding to Bcl-2 and Bcl-XL, and relatively weak affinity for Mcl-1, obatoclax mesylate demonstrates lower affinity against a broader spectrum of Bcl-2 family members including Mcl-1. This may have relevance for SCLC, which can express Mcl-1 and its pro-apoptotic partner Noxa [25,26]. Obatoclax mesylate may also have cytotoxic effects independent of Bcl-2 family member interaction. Whether relative intratumoral expression of Bcl-2 family members is clinically important in stratifying patients responsive to obatoclax mesylate awaits correlative studies.

Preliminary results have been reported from another phase I trial in which obatoclax was combined with carboplatin (AUC 5, day 1) and etoposide (100 mg/m^2, days 1–3) in patients with extensive-stage (ES)-SCLC [27]. As in the current study, reversible, infusion-related

neurotoxicity was the primary AE. The MTD of obatoclax in this study was 30 mg/m^2 on days 1–3 of an every 3-week cycle with standard doses of etoposide and carboplatin. At this dose and at one dose level below it, 7/7 patients with untreated ES-SCLC developed a PR. While this exceeds the overall response rate to first-line platinum-based therapy in patients with ES-SCLC, less robust results were seen with patients treated at similar doses with a 24-h infusion (3/6 PR). The efficacy of this regimen is being tested in an ongoing randomized phase II trial of this regimen.

In conclusion, obatoclax mesylate given IV at a dose of 14 mg/m^2 on days 1 and 3 in combination with IV topotecan at 1.25 mg/m^2 on days 1–5 of an every 3-week cycle is a safe and well-tolerated regimen in patients with relapsed solid tumor malignancies. Based on the recommended phase II dose from this study, a phase II, open-label, single-arm trial studying the efficacy of obatoclax mesylate with topotecan in patients with relapsed SCLC has been opened, and is currently accruing patients.

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Table 1

Dose escalation scheme

	Obatoclax mesylate	**Topotecan (mg/m^2)**	**Patients (*N*)**
Level 1	14 mg/m^2	1.25	6
Level 2	14 mg/m^2 day 1 and 3	1.25	3
Level 3	20 mg/m^2	1.25	5

Table 2

Patient characteristics

Characteristic	No. patients
Number of patients	14
Median age, years (range)	57 (26–74)
Gender	
Male	7
Female	7
Median KPS (range)	80% (70–90%)
Median number of prior therapies	2
Tumor type	
SCLC	8
Extrapulmonary small cell	3
Carcinoid	1
Merkel cell	1
Melanoma	1

Table 3

Dose-limiting toxicities

Toxicity	**14 mg/m^2 (*N* = 6)**	**14 + 14 mg/m^2 (*N* = 3)**	**20 mg/m^2 (*N* = 5)**
Febrile neutropenia	0	0	1 (20%)
Somnolence	0	0	1 (20%)
Mood alteration	0	0	1 (20%)
Ataxia	0	0	1 (20%)
Speech impairment	0	0	1 (20%)

Table 4

All adverse events by dose level

Toxicity	Grade 1/2[a]	Grade 3/4[a]	Grade 1/2[b]	Grade 3/4[b]	Grade 1/2[c]	Grade 3/4[c]
Hematologic						
Thrombocytopenia	–	1 (16)[d]	–	1 (33)[d]	1 (20)	2 (40)[d, e]
Anemia	1 (16)	1 (16)	1 (33)	1 (33)	2 (40)	3 (60)
Neutropenia	1 (16)	2 (33)	–	1 (33)	–	1 (20)[d]
Febrile neutropenia	–	–	–	–	–	1 (20)
Bleeding	–	–	2 (66)	–	–	–
Non-hematologic						
Fatigue	2 (33)	–	3 (100)	–	1 (20)	–
Nausea	2 (33)	1 (16)	1 (33)	–	3 (60)	–
Pain	–	–	1 (33)	–	1 (20)	–
Allergy	–	–	–	–	1 (20)	–
Alopecia	1 (16)	–	–	–	–	–
GFR	1 (16)	–	–	–	–	–
Hypoxia	–	–	–	–	1 (20)	–
LFT abnml	–	–	–	–	1 (20)	–
Neurologic						
Ataxia	5 (83)	–	2 (66)	–	3 (60)	1 (20)
Mood alteration	3 (50)	–	–	–	3 (60)	1 (20)
Somnolence	4 (66)	–	1 (33)	–	2 (40)	1 (20)
Vision changes	–	–	–	–	1 (20)	–
Dizziness	–	–	1 (33)	–	2 (40)	–
Psychosis	1 (16)	–	–	–	–	–
Restless leg	1 (16)	–	–	–	–	–
Speech impairment	–	–	1 (33)	–	–	1 (20)
Cognitive disturbance	–	–	1 (33)	–	2 (40)	–
Agitation	–	–	1 (33)	–	–	–
Personality	–	–	1 (33)	–	–	–
Memory loss	–	–	–	–	1 (20)	–

[a] 14 mg/m^2 (N = 6)

[b] 14 + 14 mg/m^2 (N = 3)

[c] 20 mg/m^2 (N = 5)

[d] Thrombocytopenia and neutropenia were the only grade 4 events

[e] One episode each of grade 3 and grade 4 thrombocytopenia